Patent
Attorney's Docket No. 032751-066

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	
Pierre LEROY	Group Art Unit: unassigned
Application No.: Continuation of Application Serial No. 08/809,110	Examiner: unassigned
Filed: August 13, 2001	
For: NOVEL IMPLANT AND NOVEL VECTOR FOR THE TREATMENT OF ACQUIRED DISEASES	

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Prior to examination on the merits, please amend the above-captioned application as follows:

IN THE SPECIFICATION:

In compliance with 37 C.F.R. § 1.823(a), please insert the attached copy of the "Sequence Listing" after the last page of the above-identified application to replace the Sequence Listing identified on pages 39-51.

Please delete pages 39-51 and renumber the application pages accordingly.

Please append the Abstract, attached on a separate piece of paper, to the end of the disclosure.

IN THE CLAIMS:

Please cancel claims 3, 8, and 13-34 without prejudice or disclaimer of the subject matter disclosed therein.

Please replace claims 1-2, 4-7, and 9-12 as follows:

1. An implant of genetically modified cells comprising an exogenous nucleotide sequence encoding all or part of an antibody directed against a tumor antigen or an epitope specific for an infectious and pathogenic microorganism, said exogenous nucleotide sequence being place under the control of elements necessary for its expression and for the secretion of said antibody, wherein said antibody is modified by fusion to a toxic or immunopotentiating substance, said antibody being functional and produced at levels of at least 50 ng/ml after reimplantation of said implant in an organism.

2. The implant according to Claim 1, wherein said antibody is selected from the group consisting of:

- a native antibody,
- a chimeric antibody
- an antibody fragment, especially a fragment Fab, $F(ab')_2$, Fc, or scFv, and
- a bispecific antibody.

4 The implant according to Claim 1, wherein said antibody is modified by fusion to a toxic substance selected from a ribonuclease, and especially the ribonuclease from Bacillus amyloliquefaciens, ricin, diphtheria toxin, cholera toxin, herpes simplex virus thymidine kinase, cytosine deaminanse from *Escherichia coli* or from a yeast of the genus *Saccharomyces*, exotoxin from *Pseudomonas* and human angiogenin or an analog of said substances.

5. The implant according to Claim 1, wherein the cells are genetically modified by transfection of a plasmidic, retroviral, herpetic, from an adenoviral, adenovirus-associated virus vector comprising said exogenous nucleotide sequence placed under the control of the elements necessary for its expression and for the secretion of said antibody.

6. The implant according to Claim 5, wherein said vector is dicistronic.

7. The implant according to Claim 6, wherein said vector is retroviral and comprises from 5' to 3':

(a) a 5' retroviral LTR,

(b) an encapsidation region,

(c) an exogenous nucleotide sequence comprising:

- an internal promoter,
- a first sequence encoding the heavy chain of an antibody,
- a ribosome entry initiation site,

- a second sequence encoding the light chain of an antibody, and

- a third sequence encoding a toxic or immunopotentiating substance fused downstream and operably to the second sequence; and,

(d) a 3' retroviral LTR.

9. The implant according to Claim 1, comprising genetically modified autologous cells.

10. The implant according to Claim 9, comprising genetically modified fibroblasts.

11. The implant according to Claim 1, comprising from 10^6 to 10^{12} genetically modified cells.

12. A method for the preparation of an implant according to Claim 1, said method comprising contacting the genetically modified cells with an extracellular matrix.

Please add claims 35-36 as follows:

35. The implant according to Claim 1, wherein said exogenous nucleotide sequence encodes the signal sequence and the extracellular I and II domains of the CD4

protein operably fused to the constant γ3 region (hinge region-CH2 and CH3) of the heavy chain of the 2F5 antibody.

36. The implant according to Claim 1 wherein said exogenous nucleotide sequence encodes the signal sequence and the extracellular I and II domains of the CD4 protein operably fused to the constant γ3 region (hinge region-CH2 and CH3) of the heavy chain of the 2F5 antibody and operably fused to the mature human angiogenin.

REMARKS

Entry of the foregoing and prompt and favorable consideration of the subject application is respectfully requested.

By the present amendment, the paper copy of the Sequence Listing for the subject application is added after the last page of the application to replace the sequence listing identified on pages 39-51. Pages 39-51 are deleted and the application pages are renumbered accordingly. A Request to Use the Computer Readable Form From Parent Application Pursuant to 37 C.F.R. § 1.821(e) and a Declaration Pursuant to 37 C.F.R. § 1.821 - .825 are being filed concurrently herewith.

A copy of the Abstract is submitted herewith on a separate piece of paper to be appended at the end of the disclosure.

Claims 3, 8, and 13-34 are canceled without prejudice or disclaimer of the subject matter disclosed therein.

Claims 1-2, 4-7, and 9-12 are amended to eliminate multiple dependency, to place them in better condition for U.S. patent practice, and to more clearly describe the claimed invention. Support for the amendments may be found throughout the application and in the claims as originally filed.

New claims 35 and 36 are added. Support for new claims 35 and 36 can be found at least at page 13 and in the Examples beginning at page 22.

Respectfully submitted,

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APPENDIX

Marked up Claims

1. [Implant] An implant of genetically modified cells comprising an exogenous nucleotide sequence encoding all or part of an antibody directed against a tumor antigen or an epitope specific for an infectious and pathogenic microorganism, [the] said exogenous nucleotide sequence being place under the control of [the] elements necessary for its expression and for the secretion of [the said antibody.] said antibody, wherein said antibody is modified by fusion to a toxic or immunopotentiating substance, said antibody being functional and produced at levels of at least 50 ng/ml after reimplantation of said implant in an organism.

2. [Implant] The implant according to Claim 1, [characterized in that the] wherein said antibody is selected from the group consisting of:

- a native antibody,
- a chimeric antibody
- an antibody fragment, especially a fragment Fab, $F(ab')_2$, Fc, or scFv, and
- a bispecific antibody.

4 [Implant] The implant according to Claim [3, characterized in that the] 1, wherein said antibody [may be] is modified by fusion to a toxic substance selected from a ribonuclease, and especially the ribonuclease from Bacillus amyloliquefaciens, ricin, diphtheria toxin, cholera toxin, herpes simplex virus thymidine kinase, cytosine deaminanse from *Escherichia coli* or from a yeast of the genus *Saccharomyces*, exotoxin from *Pseudomonas* and human angiogenin or an analog of [the] said substances.

5. [Implant] The implant according to [one of Claims 1 to 4, characterized in that] Claim 1, wherein the cells are genetically modified by transfection of a [vector derived from a plasmid, from a retrovirus or from a herpes virus, from an adenovirus,

from an] plasmidic, retroviral, herpetic, from an adenoviral, adenovirus-associated virus vector comprising [the] said exogenous nucleotide sequence placed under the control of the elements necessary for its expression and for the secretion of [the] said antibody.

6. [Implant] The implant according to Claim 5, [characterized in that the] wherein said vector is dicistronic.

7. [Implant] The implant according to Claim 6, [characterized in that the] wherein said vector is retroviral and comprises from 5' to 3':

(a) a 5' retroviral LTR [derived from a retrovirus],

(b) an encapsidation region,

(c) an exogenous nucleotide sequence comprising:

- an internal promoter,
- a first sequence encoding the heavy chain of an antibody,
- a ribosome entry initiation site,
- a second sequence encoding the light chain of an antibody, and

[(d) a 3' LTR derived from a retrovirus.]

- a third sequence encoding a toxic or immunopotentiating substance fused downstream and operably to the second sequence; and,

(d) a 3' retroviral LTR.

9. [Implant] The implant according to [one of Claims] Claim 1 [to 8], comprising genetically modified autologous cells.

10. [Implant] The implant according to Claim 9, comprising genetically modified fibroblasts.

11. [Implant] The implant according to [one of Claims 1 to 10, characterized in that it comprises] Claim 1, comprising from 10^6 to 10^{12} [, preferably from 10^7 to 10^{11}] genetically modified cells.

12. [Method] A method for the preparation of an implant according to [one of Claims 1 to 11, characterized in that] Claim 1, said method comprising contacting the genetically modified cells [and] with an extracellular matrix [are placed in contact].